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Review Article: A Systematic Review of the Effectiveness of Hospital- and Ambulatory-Based Management of Multidrug-Resistant Tuberculosis

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Abstract. A systematic review of the literature was conducted on the effectiveness of MDR-TB management. A meta-analysis of treatment outcomes of patients treated in hospitals versus ambulatory-based models was performed in accordance with PRISMA guidelines. The pooled treatment success rate was 66.4% (95% confidence interval [CI] 61.4–71.1%), with no statistical difference between ambulatory (65.5%; 55.1–74.6%) and hospital-based models (66.7%; 61.0–72.0%). The pooled death rate was 10.4% (6.3–16.5%), the pooled treatment failure rate was 9.5% (7.3–12.4%), and the defaulter rate was 14.3% (10.5–19.1%). None of the differences between the two models were statistically significant for any of the outcomes considered. This work improves the quality of the evidence available supporting the World Health Organizations (WHO) recommendation that patients be treated using mainly ambulatory care, conditional on infection control measures in the home and clinic, clinical condition of the patient, availability of treatment support to facilitate adherence to treatment, and provisions for backup facility to manage patients who need inpatient treatment care.

BACKGROUND

There are 150,000 people thought to have died of multidrug-resistant tuberculosis (MDR-TB) in 2008 alone[1]; the prevalence of MDR-TB was estimated at 650,000 cases globally in 2010.[1] Less than 5% of TB patients were tested for MDR-TB in 2010, and only 16% (46,000) of the 290,000 cases of MDR-TB that should have been tested and found among notified TB patients in 2010 were actually enrolled in treatment.

The main barriers to rapidly expanding access to diagnosis and treatment of MDR-TB in the health care system include, among others: the lack of quality assurance in laboratories for culture and drug susceptibility testing; the limited availability of quality assurance second-line anti-TB drugs, which remain a high cost; the unregulated use of anti-TB drugs in the private sector; and the limited human resources available to deliver treatment and care during the 2 years of therapy.[2] An additional barrier is the policy used in many countries of hospitalizing patients for delivery of the intensive phase of treatment (usually lasting at least 6 months), which increases costs and creates long waiting lists caused by the absence of enough hospital bed capacity.

The rationale often presented by national TB control programs for this policy is that direct observation of treatment and proper management of adverse drug reactions during hospitalization results in better treatment outcomes than ambulatory management during the full course of treatment.

A recent systematic review of the cost-effectiveness of ambulatory versus hospital-based management of MDR-TB shows there is no significant difference in treatment outcomes, the ambulatory model of care is a much lower cost and, therefore, of greater cost-effectiveness.[3] That review was, however, limited to three economic evaluations undertaken in four settings.

This systematic review summarizes evidence on the effectiveness of the ambulatory as compared with hospital-based management of the intensive phase of MDR-TB treatment from a wider range of settings. It is expected that the findings of the review will be used to inform policies that contribute to more rapid access of patients to health services for MDR-TB.

METHODS

A systematic review and meta-analysis were performed in accordance with PRISMA guidelines.[4]

Systematic review. An exhaustive search of primary studies in databases was carried out using the key words: MDR-TB AND management. We have initially used the terms "chemotherapy" and "treatment" but we have obtained a large number of studies that were mostly clinically oriented. On the other hand, the term "management" has narrowed the search to those applying programmatic management of drug-resistant tuberculosis (PMDT). Therefore, we preferred to use the term "management" in addition to "chemotherapy" or "treatment" to retrieve a larger number of studies that fulfill the inclusion criteria.

The following databases were searched: Pubmed (Medline), National Library of Medicine (NLM) Gateway, Drug Abuse Resistance Education (DARE) Database, Cochrane Controlled Trial Register, Scopus Database, and Excerpta Medica Database (EMBASE).

These databases contain articles in languages other than English but not grey literature[5]; some country experiences might have been missed by restricting the search to peer-reviewed journals.

All citations were exported into the reference manager software, "Endnote: www.EndNote.com" to keep track of citations and those that were excluded and why. The accumulated citations were then reviewed and screened.

Study selection. Population, Intervention, Comparison, and Outcome (PICO) characteristics used for study selection were the following: MDR-TB cases, receiving chemotherapy with or without surgery, hospital- or ambulatory-based treatment, and with treatment outcomes as defined below. Chemotherapy could be provided according to either a hospital-based or ambulatory-based management model, and according to either an individualized or standardized treatment strategy.

All patients diagnosed with MDR-TB were diagnosed by external quality-assured laboratories. For only two,[6,7] it was not possible to obtain a response from the contacted authors to confirm that diagnosis was quality assured.

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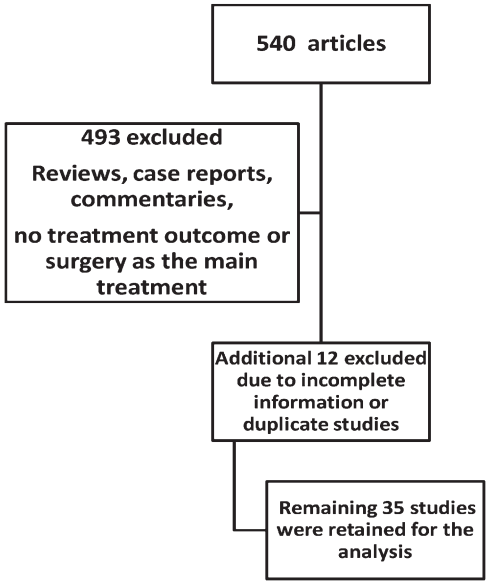

FIGURE 1. Flowchart showing the process of selecting the studies for the review.

Figure 1 shows the process of selecting the different studies. Of 540 screened articles, 35 were retained for the final analysis.

Exclusion criteria. Using the PICO characteristics, the excluded studies were the following:

Population. Any type of drug resistant TB and not MDR-TB, XDR-TB, risk factors of drug resistance among drug sensitive TB, studies reporting drug resistance surveys results among TB patients.

Intervention. Lack of information about the type of anti-TB drugs used, lack of adherence to the treatment guidelines (at least four second-line drugs (SLD) with regimens incorporating injectables during the intensive phase and fluoroquinolones, and direct observation of treatment (DOT)), treatment outcome by type of model (hospital or ambulatory). Lack of details about the type of surgery was not considered an exclusion criterion.

Comparison. No specific exclusion criteria were used.

Outcome. Lack of information about the treatment outcome according to the national or World Health Organization (WHO) guidelines. If national guidelines were not in line with WHO guidelines, they were described in the results section among the study findings.

Definitions. *Multidrug-resistant tuberculosis* is defined as TB caused by strains of *Mycobacterium tuberculosis*, which are resistant to at least isoniazid and rifampin, the two most effective drugs to treat the disease.[1]

Model of management.

- Hospital-based management: MDR-TB cases that are hospitalized for the main purpose of the delivery of the intensive phase of treatment or until culture conversion.
- Ambulatory-based management: MDR-TB cases that receive the treatment on an ambulatory basis during the full course of treatment. This might entail a short initial admission of < 1-month duration in the hospital for medical evaluation. Treatment support is provided by a health worker, community volunteer, or family member.

Type of regimen.

- Individualized treatment: Each regimen is designed on the basis of previous history of anti-TB treatment and/or individual drug susceptibility (DST) results.[8]
- Standardized treatment: Regimens are designed on the basis of representative drug resistance survey data for specific treatment categories. However, suspected MDR-TB is confirmed by DST results whenever possible. All patients in a defined group or category receive the same treatment regimen.[8]

Treatment outcome definitions used. *Cure.* Cure was defined as five consistently negative cultures for the final 12 months of treatment (nine studies). In one of the studies, it was added that a single positive culture was allowed if followed by three negative cultures, at least 30 days apart (in line with WHO guidelines).[7] Other definitions of cure were used in the different studies (Tables 1–4).

Treatment completion. Completion of the treatment course without bacteriologic documentation of cure (in line with WHO guidelines).[8]

Failure. Two or more positive sputum cultures toward the end of treatment (or a case that defaulted after 12 months of treatment with persistently positive sputum cultures) (in line with WHO guidelines).[8]

Death. Death from any cause (TB or non-TB) during the course of chemotherapy (in line with WHO guidelines).[8]

Defaulting. A patient who had interrupted treatment of two consecutive months or more and who never returned for treatment (in line with WHO guidelines).[8]

Transferred out. A patient who had been transferred out to other health institutions during treatment and for whom the treatment outcome is unknown (in line with WHO guidelines).[8]

DST methods reported in the different studies.

- The proportion method on Löwenstein-Jensen (L-J) medium (majority of studies);
- The modified absolute concentration method with 99% growth inhibition using Middlebrook 7H10 culture medium to determine sensitivity;
- Pyrazinamide susceptibility with use of the pyrazinamidase test or Wayne method in Dubos media;
- BACTEC (Becton Dickinson Diagnostic Instrument Systems, Towson, MD) for first-line drugs (FLD) except for rifabutin for most isolates and with the standard proportion method with Middlebrook 7H10 media for both first- and second-line drugs for all isolates (few studies); and
- The critical concentrations of FLD and SLD were generally standardized.

The techniques used for culture and DST, case management practices including regimens used, drug formulations and dosages, monitoring response to treatment and adverse effects, treatment support delivered to the patients, definitions adopted for treatment outcome results, were described in each setting and compared with the international guidelines.[7]

Meta-analysis. Meta-analysis of treatment outcome results was carried out using Comprehensive Meta-analysis software version 2.2 055 (Biostat Inc., Englewood, NJ; 1998–2005).

The analysis was performed on unmatched groups in prospective studies. The effect size data were selected using "event rates and sample size." The point estimate (event rate), 95% confidence interval (CI), Z test, and *P* value were calculated for each individual study and pooled across the two management models using all studies.

TABLE 1
Profile of multidrug-resistant tuberculosis (MDR-TB) management in the hospital-based settings

Author, country	No. of MDR-TB (cohorts)	% Previously treated	% HIV-positive	No.* of resistant drugs	No.* of drugs in regimen/regimen	Surgery
Goble 1993[9]	167 (1973–1983)	100%		6	4; individualized	No
Park 1998, South Korea[10]	107 (1993–1996)	100%	0%	4.2	5,4,3; individualized, mainly: Z; Pto; Cs; Ofx; PAS; amninoglycoside	No
Geerlings 2000, Netherlands[11]	44 (1985–1998)	34%	0%	5	6 (4–9); individualized	Yes
Narita 2001 USA [12]	39 (1994–1999)		41%	6 (3–11)	5 (3–10); individualized	Yes
Tahaoglu 2001, Turkey[6]	158 (1992–1999)	100%	0%	4.4 (2–9)	5.5 (3–9); individualized	Yes
Bartu 2003, Czech republic[7]	40 (2001–2004)	53%	0%	4.7	4.5 (0–6); individualized	No
Samman 2003, Saudi Arabia[13]	147 (1993–1999)		0%		Individualized	No
Palmero 2004, Argentina[14]	141 (1996–1999)	64%	0%	4.1 (2–7)	4.2 (3–5); standardized: Ofx; Cfx; Cs; Eto; S; Km; Am; Cm, PAS; E; Z	Yes
Park 2004, South Korea[15]	142 (1998–2000)	100%	0%	3 (2–4) FLD and 1 (0–6) SLD	Standardized: 2 regimens: 3 M (Z; aminoglycoside; Ofx; Pto; Cs) + 3 M (aminoglycoside; Ofx; Pto; Cs) or 6 M (aminoglycoside; Ofx; Pto; Cs; PAS)	Yes
Leimane 2005, Latvia[16]	204 (2000)	73%	0.5%	4 (2–7)	5.6 (3–8); individualized	Yes
Olle-Goig 2005, Spain[17]	143 (1983–1993)	72%		2.8	Individualized	No
Holtz 2006, Latvia[18]	167 (2000)	74%		5	5.6 (4–8); individualized	Yes
Munsiff 2006, USA[19]	574 (1992–1997)	92%	60%	5 (2–10)	8 (2–15); individualized	No
Nathason 2006, Estonia, Latvia, Peru, Philippines, Tomsk[20]	904 (1999–2001)	87%	1.70%	–	5.7; individualized	Yes
Cox 2007, Uzbekistan[21]	108 (2003–2005)	100%		4.8	7 (5–10); individualized	No
Shin 2007, Russia[22]	244 (2000–2002)	100%	0%	4.7 (3–9)	5.8; individualized	Yes
Eker 2008, Germany[23]	177 (2004–2006)	53%	4.9%	36% resistant to FLD; 8% to FQ; 12.8% to injectable SLD; < 1% to Linezolid	Individualized	No
Masjedi 2008, IR Iran[24]	43 (2002–2006)	100%	0%		5,4; standardized: Ofx; Cs; Pto; Am; E or Z	No
Shean 2008, South Africa[25]	491 (1992–2002)	93%	9%	2 (2–8)	Individualized	Yes
Tupasi 2006, Philippines[26]	171 (1999–2002)	12%		62% resistant to ≥ 5 FLD	Individualized	No
Bartu 2010, France[27]	50 (2001–2009)	52%	0%	Resistance to 5 FLD in 52% of patients	Individualized	No
Brust 2010, South Africa[28]	1,261 (2000–2003)	81%	52%	74% resistant to ≥ 3 FLD	Standardized: Km, Ofx, Eto, Z, E, or Cs in case of E resistance	No
Heller 2010, South Africa[29]	57 (2008)				Individualized	No
Van Deun 2004, Bangladesh[30]	58 (1997–1999)			3.2	7,5,2; standardized	No
Van Deun 2010, Bangladesh[31]	234 (1997–2007)				Standardized; 9 M of Gati, Cfz, E, Z throughout the treatment period supplemented by Pto, Km, and high-dose H during an intensive phase of a minimum of 4 M	No
Uffredi 2006, France[32]	45 (1998–1999)	47%	20%	16% resistant to H and R and susceptible to other FLD	Individualized	Yes

*Mean/median and range; HIV = human immunodeficiency virus; M = month; FLD = first-line drugs; SLD = second-line drugs; FQ = fluoroquinolones; Z = pyrazinamide; Pto = protionamide; Cs = cycloserine; Ofx = ofloxacin; PAS = *p*-aminosalicylic acid; Eto = ethionamide; S = streptomycin; Km = kanamycin; Am = amikacin; E = ethambutol; Gati = gatifloxacin; H = isoniazid; R = rifampicin.

TABLE 2
Profile of multidrug-resistant tuberculosis (MDR-TB) management in the hospital-based settings

Author, country	Time to initiation of treatment (IT); sputum conversion (SC); culture conversion (CC)	Total treatment duration	DOT	Treatment success rate	Definition of cure
Goble 1993[9]		7 M	IP only	48% (41–55)	Culture negative for 3 consecutive months
Park 1998, South Korea[10]	CC: mean 2 M (range 1–10 M)	24 M	IP only	82.5%	Culture negative for 18 months
Geerlings 2000, Netherlands[11]		20 M (9–54)	No	75%	≥ 2 M of consecutive negative culture
Narita 2001[12]	IT: median 177 days (26–2434) CC: median 19.5 days (672–1,897)		Yes	79%	Outcome: (completed, death, or incomplete treatment). In accordance with CDC guidelines, completion of TB treatment is documented treatment with at least two drugs to which the strain of *M. tuberculosis* is known to be susceptible, for at least 12 months after culture conversion
Tahaoglu 2001 Turkey[6]	CC: 95% after a mean of 1.9 M (1–9)	18 M	IP only	77%	Negative smears and cultures for at least 18 months
Bartu 2003, Czech republic[7]			Yes	68% (55–79)	Culture negative, no clinical evidence of tuberculosis
Samman 2003, Saudi Arabia[13]			No	81%	Resolution of radiologic changes, clinical improvement and negative culture at the end of treatment
Palmero 2004, Argentina[14]	CC: mean 5.2 M (SD: ±2.3)	18 M (SD: ±5.4)	No	81%	*
Park 2004, South Korea[15]	CC: median of 2 M (range: 1–11)	24 M	No	44%	Consistently negative culture during the last 18 months of treatment
Leimane 2005, Latvia[16]		22 M (18–30)	Yes	62%	Completion of treatment with at least three consecutive sputum samples (separated by at least a 1-month interval) with negative cultures for AFB (the third obtained during the last month of treatment) and return for at least 2 years with negative sputum cultures for AFB and no worsening of clinical condition and radiological findings at each yearly visit
Olle-Goig 2005, Spain[17]	SC: mean 69.4 days (SD: ±76) CC: mean 81.3 days (SD: ±74.6)	Mean 18 M (SD: ±9)	Yes	Cure: 44.6%, completed: 14.7%	*
Holtz 2006, Latvia[18]	SC: 83 days (range: 1–698) CC: 169 days	12–18 M	Yes	62%	*
Munsiff 2006[19]		median: 18 M (range: 1.0–37.5)	Yes	66.0%	*
Nathason 2006, Estonia, Latvia, Peru, Philippines, Tomsk[20]		24 M	Yes	67.5%	
Cox 2007, Uzbekistan[21]	42 days (28–679)	18 M (1–83)	Yes	40% (36–44%)	*
Shin 2007, Russia[22]		18–24 M	Yes	68% (64–71%)	*
Eker 2008, Germany[23]		18–43 M	No	36% (28–44%)	–
Masjedi 2008, IR Iran[24]	CC: 5 M (2–45)	17 M (1–66)	Yes	49%	*
Shean 2008, South Africa[25]	CC: 2 M (1–8)	18.5 M (1–42.4)	Yes	77%	"Cured" after 18 M of consecutive negative cultures.
Tupasi 2006, Philippines[26]	SC: 5 mean 9 M (SD: ±5.2)		Yes	72%	Completion of treatment with consistently negative cultures in the final year of treatment
Bartu 2010, France[27]			IP only	43.9%	
Brust 2010, South Africa[28]		18–24 M	IP only	Interim results at 6 M: 91.2%	Culture negative at end of treatment and 2 previous occasions
		18–24 M	IP only	63% (50–76%)	

(Continued)

Table 2
Continued

Author, country	Time to initiation of treatment (IT); sputum conversion (SC); culture conversion (CC)	Total treatment duration	DOT	Treatment success rate	Definition of cure
Heller 2010, South Africa[29]	IT: 106.5 days (88.6–151.1) SC: 91 days (72.2–119.8) CC: 119 days (106.1–131.9)				Culture negative at end of treatment and 2 previous occasions
Van Deun 2004, Bangladesh[30]		12 M	–	58%	
Van Deun 2010, Bangladesh[31]		9 M		Relapse-free cure of 87.9% (95% CI: 82.7–91.6)	
Uffredi 2006, France[32]		12 M		58%	

*Five consistently negative culture results for the final 12 months of treatment.
CI = confidence interval; M = month; IP = intensive phase; SC = sputum conversion; CC = culture conversion; DOT = direct observation of treatment; AFB = acid fast bacilli.

We present results using both random and fixed effects models whenever appropriate. The fixed-effect model assumes there is one true effect size, which underlies all the studies in the analysis, and that any differences in observed effects are caused by sampling error. Given the implausibility of this assumption, the random effects model is generally preferred in our discussion of results.

The relative weight of the studies was determined by their individual sample size. Those having a larger sample size had higher weights compared with others. The relative weights assigned under random effects are more balanced than those assigned under fixed effects.

The following variables were used as moderators to adjust for their confounding effect on the treatment outcomes: proportion of previously treated patients tested for FLD susceptibility testing, prevalence of human immunodeficiency virus (HIV) among tested TB patients, number of SLD used in the regimen, treatment duration, surgery for MDR-TB, and direct observation of treatment during the intensive and continuation phase.

TABLE 3
Profile of multidrug-resistant tuberculosis (MDR-TB) management in the ambulatory-based settings

Author, country	No. of MDR-TB (cohorts)	% Previously treated	% HIV-positive	No.* of resistant drugs	Setting details	No.* of drugs in regimen/regimen	Surgery
Kim 2001, Korea[33]	1,175 (1988–1996)	100%		3.7	Chest clinic	5.3; individualized	Yes
Ward 2005, Vietnam[34]	44 (1989–2000)	77%	0%	Median: 4.5	Ambulatory DOT at 3 locations	8 (6–12); standardized	No
Malla 2009, Nepal[35]	175 (2005–2006)	98%		73.1% resistant to HRSE, 17% to HRS, 6.3% to HRE, 2.9% only to HR		Standardized	No
Thomas 2007, India[36]	66 (1999–2003)	100%		18% resistant to HR, 52% to one or two FLD in addition to HR (S/E), and 30% resistant to one or more SLD		Individualized	No
Mitnick 2003, Peru[37]	75 (1996–1999)	100%	1.50%	Median: 5 (2–5) FLD and 1 (0–7) SLD		6 (5–9); individualized	
Narita 2001, USA[12]	31 (1994–1997)		48%	Median: 3 (2–8)		3 (0–5): individualized	No
Heller 2010, South Africa[29]	50 community-based				Initial 4 weeks of hospitalization then ambulatory DOT in the PHCs close to home	Individualized	No
Saravia 2005, Peru[38]	73 (2005)	None of the 74				Standardized	No
Saravia 2005, Peru[38]	52 (2005)					≥ 5: individualized	No

*Mean/median and range; M = month; FLD = first-line drugs; SLD = second-line drugs; FQ = fluoroquinolones.

TABLE 4
Profile of multidrug-resistant tuberculosis (MDR-TB) management in the ambulatory-based settings

Ambulatory-based studies	Time to initiation of treatment (IT); sputum conversion (SC); culture conversion (CC)	Total treatment duration*	DOT	Treatment success rate	Definition of cure
Kim 2001, Korea[33]	CC: 2.1 M (±3.4), range (1–13)	23 M (±3.4)	No	48.2%	2 or more sputum culture negative at the end of treatment
Ward 2005,Vietnam[34]	SC: 14.8 M (6–51) CC: mean 23.0 (SD: ±11.4)	23.0 (SD 11.4) M	Yes	86%	15 consecutive M of smear negative sputum
Malla 2009, Nepal[35]	CC: 24 M	24 M	Yes	70%	*
Thomas 2007, India[36]	CC: 90% by 4th M	At least 12–18 M after the culture negativity	Under partial supervision i.e., three times a week	38%	Completion of at least 18 M of treatment and culture negative for the final 12 consecutive months
Mitnick 2003, Peru[37]	TI: 8.1 M (0.2–103.2) SC: 38 days (14–264) CC: 35 days (23–181)	23 M (0.4–35.9)	Yes	83%	Completion of at least 12 M of treatment with consecutive negative cultures
Narita 2001[12]	TI: 15 days (106–276) CC: 39 days (33–211)		Yes	48%	As defined in Table 2
Heller 2010, South Africa[29]	TI: 84 days (95% CI: 78.7–93.3) SC: 59 days (95% CI: 34.9–83.1) CC: 85 days	Not completed	Yes	Interim: 84.8%	As defined in Table 2
Saravia 2005, Peru[38]		18 M	Yes	43.6%	Negative culture in the last 3 M of therapy or at M 18
Saravia 2005, Peru[38]		18–24 M	Yes	79%	Negative culture in the last 3 M of therapy or at M 18

*Five consistently negative culture results for the final 12 months of treatment.
CI = confidence interval; M = month; IP = intensive phase; SC = sputum conversion; CC = culture conversion; DOT = direct observation of treatment.

Heterogeneity tests were applied to assess the extent and type of variations between studies such as Q-test, I-square, Tau-square. A funnel plot was used to assess for the publication bias and the latter was adjusted for using the Duval and Tweedie's trim and fill test.

RESULTS

Description of studies. The 35 studies that were retained for final analysis reported treatment outcome results for a total of 14,478 patients receiving SLD treatment of MDR-TB. These patients were treated during the period 1973–2007 and the studies were published during the period 1993–2010.

The 35 studies were categorized as follows: 27 hospital-based MDR-TB management studies published in 25 articles and 8 ambulatory-based MDR-TB management studies. A direct comparison between hospital and ambulatory-based management of MDR-TB had been carried out in only one study. Of the 26 studies that followed individualized regimens, 21 were hospital-based models and the rest ambulatory. Of the nine studies that followed standardized regimens, six were hospital-based and the rest ambulatory.

The studies were reported from 22 countries: 4 from South Africa, 4 from the United States, 3 from Peru, 3 from South Korea, and 2 each from Bangladesh, the Czech Republic, and Latvia. The remaining countries reported one study each: Argentina, Estonia, France, Germany, India, Iran, Nepal, Netherlands, Philippines, Russia, Saudi Arabia, Spain, Turkey, Uzbekistan, and Vietnam.[9–38] A detailed description of the studies is shown in Tables 1–4.

Tables 1 and 2 show the details of the 27 studies reporting a hospital-based management model. In seven studies all of the treated MDR-TB cases detected were among previously treated TB cases. The HIV testing results were reported in the majority of studies and the HIV prevalence was generally between 0% and 1%, but higher in South Africa (52%)[28] and the United States (41–60%).[12,19]

Most of the studies reported resistance to three or more FLD and MDR-TB regimens used consisted of at least four drugs. In 11 studies, surgery was used as adjuvant to chemotherapy.

Time to initiation of treatment or to sputum conversion was seldom reported (three and four studies, respectively). The median/mean time to treatment initiation ranged between 42 and 177 days, whereas the median/mean time to sputum smear conversion ranged from 69 days to 5.9 months. On the other hand, time to culture conversion was reported in 10 studies, and the median/mean time ranged from 2 to 5 months. The median/mean treatment duration was ≥ 18 months for the majority of the studies (N = 15), and four studies reported smaller durations: 7 months in the United States in 1993, 12 months in Latvia and France, 17 months in South Africa, and 9 months in Bangladesh. The DOT was not applied in five settings during the intensive phase, and in 11 during the continuation phase. Treatment success rate ranged from 36% to 82.5% in the hospital model.

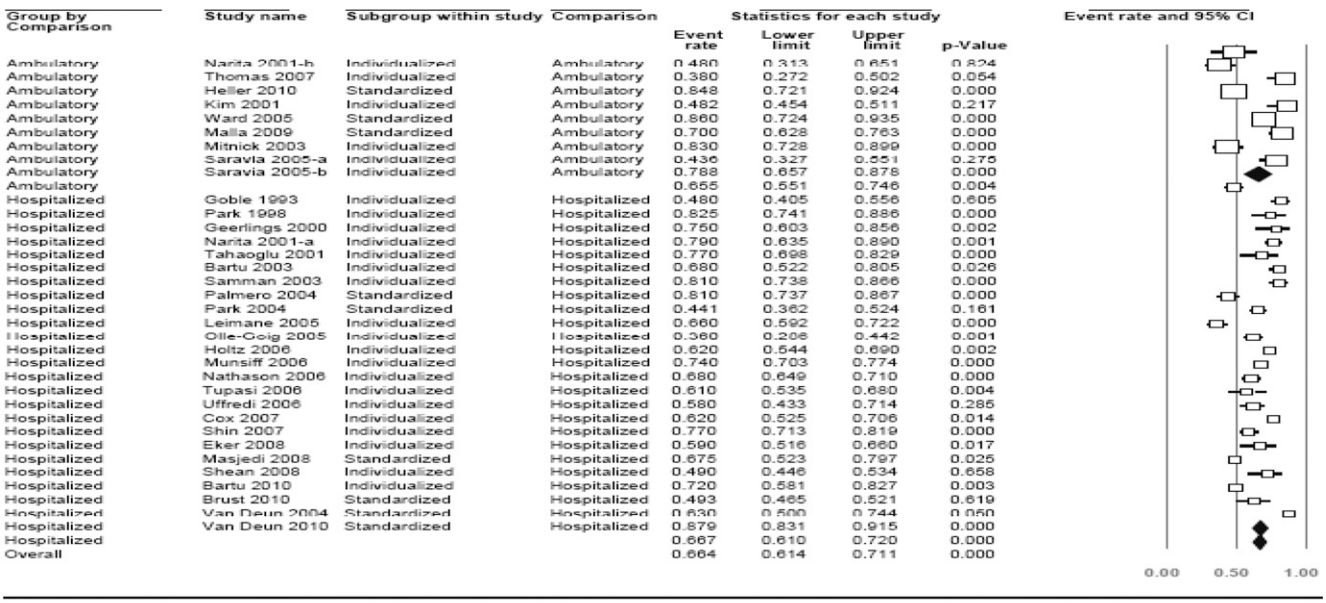

FIGURE 2. Meta-analysis of the treatment success rate in hospitalized and ambulatory-based setting.

Tables 3 and 4 show the details of the eight ambulatory-based management studies of MDR-TB. In three studies only, all the treated MDR-TB cases were detected among previously treated TB cases. The HIV testing results were reported in three studies only and the HIV prevalence was between 0% and 1.5% in two studies and 48% in the third. Most of the studies reported resistance to three or more FLD and MDR-TB regimens used consisted of at least five drugs except in one study where the mean number of drugs used was three. In one study only, surgery was used as adjuvant to chemotherapy according to well-defined eligibility criteria.

Time to initiation of treatment or to sputum conversion was reported in three studies. The median/mean time to treatment initiation ranged between 15 days and 8 months, whereas the median/mean time to sputum smear conversion ranged from 38 days to 14.8 months. On the other hand, time to culture conversion was reported in the majority of the studies, and the median/mean time ranged from 35 to 85 days.

The median/mean treatment duration was ≥ 18 months in all the studies. The DOT was ensured during the intensive and continuation phase except for two studies. In a Korean study, drugs were given monthly; interruptions resulted in telephone calls or postcards. In an Indian study, drugs were given under partial supervision, i.e., three times a week when patients attended for injection, oral drugs were given under supervision and the next day's dose was supplied for self administration. Treatment success rate ranged from 38% to 84.8% in the ambulatory model.

Pooled estimates of treatment outcomes. Figure 1 shows a pooled treatment success rate of 66.4% (95% CI, 61.4–71.1%), with no statistical difference between the ambulatory model (65.5%; 55.1–74.6%) and the hospital-based model (66.7%;

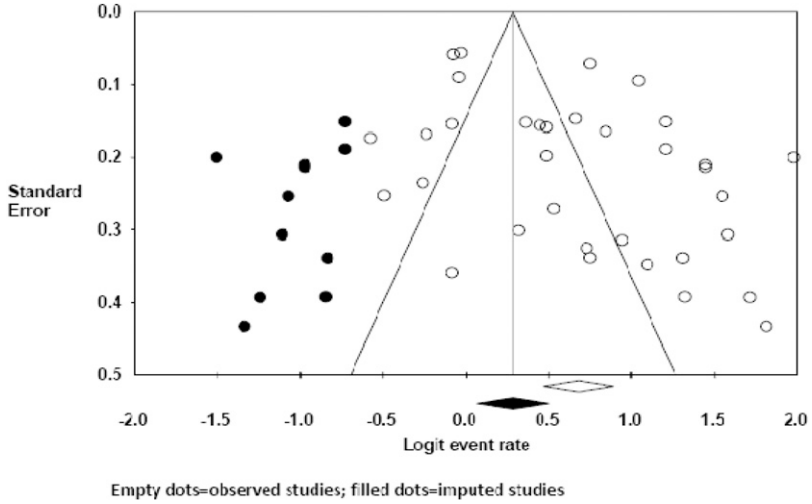

FIGURE 3. Funnel plot of standard error by logit event rate.

TABLE 5
Adjustment of the pooled estimates for treatment success rate*

		Fixed effects			Random effects			
	Studies trimmed	Point estimate	Lower limit	Upper limit	Point estimate	Lower limit	Upper limit	Q-value
Observed values		0.59388	0.58228	0.60538	0.66377	0.61528	0.70904	524.20397
Adjusted values	5	0.58416	0.57269	0.53553	0.62732	0.57812	0.67401	619.32148

*Using Duval and Tweedie's trim and fill.

61.0–72.0%). Regarding unfavorable treatment outcomes, the pooled death rate was 10.4% (6.3–16.5%), and it was lower in ambulatory models (7.8%, 5.2–11.7%) compared with the hospital-based models (12.9%; 10.3–16.0%). The pooled treatment failure rate was 9.5% (7.3–12 4%), and was higher in the ambulatory models (11.4%, 6.7–18.8%) compared with the hospital-based model (9.0%; 6.5–12.2%). On the other hand, the defaulter rate was 13.3% (7.5–22.6%) and 14.7% (10.2–20.7%) in the ambulatory and hospital-based models, respectively, with a pooled rate of 14.3% (10.5–19.1%). None of these differences are significant at the 95% level of confidence.

Heterogeneity tests. Heterogeneity tests showed significant variations between studies, where Q-value, the weighed sum of squares (WSS) on a standardized scale was significantly different compared with expected WSS. This value shows the excess variance (Q = 542.2, $P = 0.0$). I-squared showed that 93.9% of the observed dispersions are attributed to real rather than spurious variations. The variance of the true effect was 0.337 (Tau-squared = 0.337).

Publication bias and adjustment of the pooled estimate. The funnel plot showed evidence of bias with most of the studies missing at the bottom rather than around the main effect. The imputed studies were mainly to the left of the bottom (Figure 3). Accordingly, the Duval and Tweedie's trim and fill test was applied to adjust for the publication bias. This resulted in adjustment of the point estimate of the treatment success rate under a random effect model from 66.4% (61.4–71.1%) to 62.7% (57.8–67.4%) (Table 5). The adjustment made for the pooled estimates of the unfavorable outcomes is shown in Table 6. Such adjustment was only needed for the pooled estimates of the death rate from 10.4% (6.3–16.5%) to 9.2% (7.3–11.5%).

DISCUSSION

In the absence of randomized trials assessing models of care for the programmatic management of MDR-TB, this review focused on observational studies selected on methods internationally established for systematic reviews and meta-analysis (reference to PRISM). Across all selected studies, the overall observed treatment success estimate was 66.4% (61.4–71.1%). Although the proportion of patients achieving treatment success was slightly higher in studies that used hospital-based MDR-TB management compared with ambulatory treatment, the difference was not statistically significant.

This point estimate is not significantly higher than the estimate reported in the latest systematic review published in 2009, which showed 62% (95% CI, 58–67%).[39] However, the adjusted estimate was comparable to this latest review. Overall, patients treated with individualized treatment regimens reported higher treatment success rates compared with those treated with standardized regimens as reported by an earlier systematic review and meta-analysis comparing the treatment outcome of the two methods.[39] It is noteworthy to mention that the reported adjusted pooled treatment success rate of 62.7% is still unacceptably low. In only one study from Bangladesh,[30] a standardized short regimen of 9-month duration containing gatifloxacin reported a relapse-free cure rate of 87.9% (82.7–91.6). Among other treatment outcomes it is also noteworthy that adherence to treatment in the continuation phase was not significantly different in the two models of care we compared. Unfortunately, the reviewed papers did not include complete data to compare smear/culture conversion in the two models assessed.

The heterogeneity in the study characteristics led to significant variation in reported treatment outcomes. This was adjusted for in the pooled estimate. However, the results were confounded by other factors that could not be adjusted in the analysis, such as the factors that influence response to treatment and, eventually, treatment outcomes, such as good general condition of the patient, presence of bilateral disease, availability of a strong social support network that delivers adequate care of the patient. The role of civil society in supporting MDR-TB patients during the whole duration of treatment of both the patient treated on the ambulatory-based model or during the continuation phase of those on hospital-based models was poorly described in the selected studies. Overall, the scanty data on these variables in the studies included in this review prevents us from inferring the direction and magnitude of their influence in the outcomes observed. The limitations related to selection bias can only be controlled in a randomized controlled trial.

This review provided some evidence that the model of care under which the MDR-TB patient receives the intensive

TABLE 6
Meta-analysis of the unfavorable treatment outcome results

	Pooled estimate (95% confidence interval)		
Setting	Death rate (%)	Failure rate (%)	Defaulter rate (%)
Hospitalized (unadjusted)	12.9 (10.3–16.0)	9.0 (6.5–12.2)	14.7 (10.2–20.7)
Ambulatory (unadjusted)	7.8 (5.2–11.7)	11.4 (6.7–18.8)	13.3 (7.5–22.6)
Overall (unadjusted)	10.4 (6.3–16.5)	9.5 (7.3–12.4)*	14.3 (10.5–19.1)*
Overall (adjusted)	9.2 (7.3–11.5)		

*No publication bias according to the funnel plot test. No adjustment is needed as there is no publication bias.

phase of treatment is not associated with treatment outcomes, and gives further support to the recommendation in the WHO 2011 MDR/TB guidelines to introduce ambulatory models. The implications of this finding are enormous for several reasons.

First, in many settings, one of the major bottlenecks to explain is that globally only 16% of the estimated number of MDR-TB cases among TB diagnosed patients is having access to treatment as a result of the limited funding available for delivering care under hospital model of care. The findings of this review suggest that, in the absence of medical or social justification for hospitalization, all MDR-TB patients could be effectively treated on an ambulatory basis. The further evaluation of this option in Eastern European countries, and subsequent policy change, could reduce substantially the cost of MDR-TB management, and increase its cost-effectiveness. In the four studies considered in a recent review of cost and cost-effectiveness of MDR-TB management, the health system costs were between US$ 237 and US$ 6791 per patient or 7% and 62% of the total cost, depending on the setting and model of care. In generalizing those results to a larger number of settings, the paper estimates that the cost per patient under outpatient models of care is about 63% (33–85%, 5th–95th percentiles) lower than under inpatient models. Unfortunately, resource use was not consistently reported in the 29 studies considered in this study—it was not a criteria for inclusion—and we have therefore not been able to present any results on cost and cost-effectiveness. However, WHO estimates of the cost to the health system of a 20-minute visit to an outpatient clinic and the cost of a bed-day[40] suggest that the latter is between 2.3 and 15.8 times more expensive in the 22 countries studied, depending on the country and type of facility in question. Given that this review does not show evidence of the greater effectiveness of hospital-based models, it is very unlikely that hospital-based models would have emerged as more cost-effective overall.

Second, the choice between hospitalization and ambulatory treatment depends on several factors in addition to the severity of the disease. Such factors include the availability of hospital beds with adequate infection control measures to prevent nosocomial transmission; the availability of trained personnel at hospitals and clinics to administer treatment and manage adverse drug reactions; the availability of a social support network to facilitate adherence to ambulatory treatment; and the presence of other clinical or social conditions in patients.

Health authorities need to take stronger measures for preventing, and not just for treating MDR-TB. The selection of an ambulatory model of care has not only implications on increasing access to treatment, but may also have profound implications in the prevention of MDR-TB by facilitating early enrollment in treatment (abolishing waiting lists) and reducing nosocomial transmission. Several studies have proven that hospitals lacking appropriate infection control measures can be a major source of DR-TB transmission.[41,42]

Third, a model of care acceptable to the patient must be grounded on solid ethics standards and with due respect to human rights. In a vast majority of settings, patients preferred to receive health care at the household or close to their families. Enforcing a model of care, like non-voluntary hospitalization or isolation, rather than providing options to meet the needs of patients, might have detrimental effects on the physical and mental well being of these patients.

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